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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/501,671	NISHIO, FUMIHIDE	
	Examiner	Art Unit	
	Sheridan R. MacAuley	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 November 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-37* is/are pending in the application.

4a) Of the above claim(s) *16,17 and 19-37* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15 and 18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Alignment 1 of SEQ ID NO:1*.

DETAILED ACTION

Claims 1-37 are pending.

Election/Restrictions

1. Applicant's election with traverse of claims 1-18 and element (a) as the species of elements, a nonionic surfactant as the species of compounds, combination 1 as the species of combinations, and SEQ ID NO: 1 as the species of peptides in the reply filed on November 5, 2007 is acknowledged. The traversal is on the ground(s) that the restriction and species election requirement is improper because it does not satisfy the requirements of PCT Rules 13.1 and 13.2. This is not found persuasive because the instantly claimed inventions do not relate to a single general inventive concept because they lack a common special technical feature that makes a contribution over the prior art. The technical feature common to the groups is a soluble thrombomodulin, which is taught by the EP1029548 reference (document cited in IDS), as discussed in the office action mailed on September 4, 2007. Furthermore, a freeze-dried (i.e. lyophilized) composition comprising a nonionic surfactant was known in the art at the time of the invention, as taught by Kunihiro et al. (US 5,834,028, abstract). Since the inventions lack a special technical feature which makes a contribution over the prior art, the restriction and species election requirements made in the office action mailed on September 4, 2007 are proper.

2. The requirement is still deemed proper and is therefore made FINAL.

3. Claims 16, 17 and 19-37 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected groups and species, there being no allowable generic or linking claim.

4. Claims 1-15 and 18, insofar as they read upon the elected species, are examined in the merits in this office action.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1-15 and 18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

7. The claims are rendered indefinite because they recite a method of inhibiting foaming of a high-concentrated thrombomodulin-containing solution by allowing the presence of a nonionic surfactant. Since the only method step that is required by the claim is the presence of the nonionic surfactant, it is unclear whether applicant intends for the nonionic surfactant to be present in the thrombomodulin-containing solution.

8. The claims are also rendered indefinite by the recitation of "a concentration of 10 mg/mL or more," for example, in line 4 of claim 1. It is unclear whether applicant intends to claim that the solution has a concentration of 10 mg/mL of thrombomodulin or a concentration of 10 mg/mL of all components.

9. The term "high-concentrated" in the claims, for example, in line 3 of claim 1, is a relative term which renders the claims indefinite. The term is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Since the claim does not clearly state what would constitute a "high" concentration, the metes and bounds of the claim would be unclear to one of ordinary skill in the art.

10. Claim 14 is further rendered indefinite by the recitation of "an existential amount." It is unclear what applicant intends to claim using the word "existential." It is recommended that applicant remove the word and amend the claim to recite, for example, that the nonionic surfactant is present at an amount of 0.01 mg or more per 10 mg of soluble thrombomodulin.

Claim Rejections - 35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. Claims 1-4, 7-9 and 12-15 are rejected under 35 U.S.C. 102(b) as being anticipated by Kunihiro et al. (US 5,834,028). Claims 1 and 2 recite a method of inhibiting foaming of a high-concentrated soluble thrombomodulin-containing solution,

which is used in preparing a high-concentrated soluble thrombomodulin-containing solution having a concentration of 10 mg/mL or more by dissolving a soluble thrombomodulin-containing freeze-dried preparation that contains soluble thrombomodulin as an active ingredient, the method being characterized by comprising at least one of: (a) allowing the presence of at least one compound selected from the group consisting of a nonionic surfactant, benzyl alcohol, and chlorobutanol. Claims 3 and 4 recite the method of claim 1, characterized by allowing the presence of a nonionic surfactant in the soluble thrombomodulin-containing freeze-dried preparation or in a dissolving aqueous solution for dissolving the soluble thrombomodulin-containing freeze-dried preparation. Claims 7 and 8 recite the method of claim 1, characterized in that the high-concentrated soluble thrombomodulin-containing solution has a soluble thrombomodulin concentration of 17 mg/mL or more, specifically 25 mg/mL or more. Claim 9 recites the method of claim 1, characterized in that a fluid volume of the high-concentrated soluble thrombomodulin-containing solution prepared by dissolution is in a range of 0.1 mL to 2 mL and an osmotic pressure ratio upon dissolution thereof is in a range of 0.5 to 2.0. Claim 12 recites a method according to claim 1, characterized in that: the soluble thrombomodulin-containing freeze-dried preparation is allowed to contain one or two compounds selected from the group consisting of arginine, glutamic acid, proline, serine, glycine, histidine, asparagine, lysine, phenylalanine, and valine, or salts thereof, trehalose, lactose, and sucrose; further, a nonionic surfactant is allowed to be present in the soluble thrombomodulin-containing freeze-dried preparation and/or in the dissolving aqueous solution for dissolving the soluble thrombomodulin-containing

freeze-dried preparation. Claim 13 recites the method of claim 1, characterized in that the nonionic surfactant comprises at least one compound selected from the group consisting of polyoxyethylene sorbitan fatty acid ester, polyoxyethylene/ polyoxypropylene copolymer, polyoxyethylene alkylether, polyoxyethylene fatty acid ester, and polyoxyethylene hydrogenated castor oil. Claim 14 recites the method of inhibiting foaming of a high-concentrated soluble thrombomodulin-containing solution according to claim 1, characterized in that the nonionic surfactant has an existential amount of 0.01 mg or more per 10 mg of the soluble thrombomodulin. Claim 15 recites the method of claim 1, characterized in that the soluble thrombomodulin comprises a peptide that can be dissolved in water in a concentration of 30 mg/mL or more.

13. Kunihiro teaches a method for preparing a lyophilized (i.e. freeze-dried) composition comprising soluble thrombomodulin and a nonionic surfactant (i.e. a surface-active agent), such as a polyoxyethylene sorbitan fatty acid ester (abstract, col. 9, lines 29-52). Kunihiro teaches that the surfactant may be present in the lyophilized preparation or in the solution that the preparation is dissolved in (col. 11, lines 15-36). In the absence of evidence to the contrary, the composition of Kunihiro may be used to prepare thrombomodulin-containing solutions of the concentrations recited in the claims and with the claimed osmotic pressure upon dissolution. Further, absent evidence to the contrary, the thrombomodulin used in the method of Kunihiro has the claimed solubility in water. Kunihiro teaches the preparations of fluids with fluid volumes of 2 milliliters (col. 20, experiment 5). Kunihiro teaches that the lyophilized composition may

comprise arginine or lactose and that the composition may be mixed with sufactant (e.g. polysorbate 80) at the claimed concentration (abstract, col. 20, experiment 5).

14. Note that a recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim.

15. Moreover, the claimed functions, characteristics, and/or traits must be inherent to the reference composition. The discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new. Thus the claiming of a new use, functions or unknown property that is inherently present in the prior art does not necessarily make the claim patentable (MPEP 2112).

16. Therefore, Kunihiro anticipates all of the limitations of the cited claims.

Claim Rejections - 35 USC § 103

17. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

18. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

19. Claims 1-4, 7-10 and 12-15 rejected under 35 U.S.C. 103(a) as being unpatentable over Kunihiro et al. (US 5,834,028) in view of JP 11-171790 (see English abstract). Claims 1 and 2 recite a method of inhibiting foaming of a high-concentrated soluble thrombomodulin-containing solution, which is used in preparing a high-concentrated soluble thrombomodulin-containing solution having a concentration of 10 mg/mL or more by dissolving a soluble thrombomodulin-containing freeze-dried preparation that contains soluble thrombomodulin as an active ingredient, the method being characterized by comprising at least one of: (a) allowing the presence of at least one compound selected from the group consisting of a nonionic surfactant, benzyl alcohol, and chlorobutanol. Claims 3 and 4 recite the method of claim 1, characterized by allowing the presence of a nonionic surfactant in the soluble thrombomodulin-containing freeze-dried preparation or in a dissolving aqueous solution for dissolving the soluble thrombomodulin-containing freeze-dried preparation. Claims 7 and 8 recite the method of claim 1, characterized in that the high-concentrated soluble thrombomodulin-containing solution has a soluble thrombomodulin concentration of 17 mg/mL or more, specifically 25 mg/mL or more. Claim 9 recites the method of claim 1, characterized in

that a fluid volume of the high-concentrated soluble thrombomodulin-containing solution prepared by dissolution is in a range of 0.1 mL to 2 mL and an osmotic pressure ratio upon dissolution thereof is in a range of 0.5 to 2.0. Claim 10 recites the method of claim 1, characterized in that the soluble thrombomodulin-containing freeze-dried preparation is allowed to contain a combination containing two of: glutamic acid or a salt thereof and mannitol. Claim 12 recites a method according to claim 1, characterized in that: the soluble thrombomodulin-containing freeze-dried preparation is allowed to contain one or two compounds selected from the group consisting of arginine, glutamic acid, proline, serine, glycine, histidine, asparagine, lysine, phenylalanine, and valine, or salts thereof, trehalose, lactose, and sucrose; further, a nonionic surfactant is allowed to be present in the soluble thrombomodulin-containing freeze-dried preparation and/or in the dissolving aqueous solution for dissolving the soluble thrombomodulin-containing freeze-dried preparation. Claim 13 recites the method of claim 1, characterized in that the nonionic surfactant comprises at least one compound selected from the group consisting of polyoxyethylene sorbitan fatty acid ester, polyoxyethylene/ polyoxypropylene copolymer, polyoxyethylene alkylether, polyoxyethylene fatty acid ester, and polyoxyethylene hydrogenated castor oil. Claim 14 recites the method of inhibiting foaming of a high-concentrated soluble thrombomodulin-containing solution according to claim 1, characterized in that the nonionic surfactant has an existential amount of 0.01 mg or more per 10 mg of the soluble thrombomodulin. Claim 15 recites the method of claim 1, characterized in that the soluble thrombomodulin comprises a peptide that can be dissolved in water in a concentration of 30 mg/mL or more.

20. Kunihiro teaches a method for preparing a lyophilized (i.e. freeze-dried) composition comprising soluble thrombomodulin and a nonionic surfactant (i.e. a surface-active agent), such as a polyoxyethylene sorbitan fatty acid ester (abstract, col. 9, lines 29-52). Kunihiro teaches that the surfactant may be present in the lyophilized preparation or in the solution that the preparation is dissolved in (col. 11, lines 15-36). In the absence of evidence to the contrary, the composition of Kunihiro may be used to prepare thrombomodulin-containing solutions of the concentrations recited in the claims and with the claimed osmotic pressure upon dissolution. Further, absent evidence to the contrary, the thrombomodulin used in the method of Kunihiro has the claimed solubility in water. Kunihiro teaches the preparations of fluids with fluid volumes of 2 milliliters (col. 20, experiment 5). Kunihiro teaches that the lyophilized composition may comprise arginine or lactose and that the composition may be mixed with sufactant (e.g. polysorbate 80) at the claimed concentration (abstract, col. 20, experiment 5). Although the reference discloses the use of mannitol as an additive to a thrombomodulin composition (col. 18, lines 5-9), Kunihiro does not specifically teach the addition of mannitol and glutamic acid.

21. JP 11-171790 teaches a method for preventing the denaturation of thrombomodulin in a freeze-dried preparation by adding mannitol and glutamic acid (see English abstract).

22. Note that a recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to

patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim.

23. Moreover, the claimed functions, characteristics, and/or traits must be inherent to the reference composition. The discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new. Thus the claiming of a new use, functions or unknown property that is inherently present in the prior art does not necessarily make the claim patentable (MPEP 2112).

24. At the time of the invention, a method for preparing thrombomodulin comprising nearly all of the claimed elements was known, as taught by Kunihiro. It was further known that mannitol and glutamic acid could be used in a similar method. One of ordinary skill in the art would have been motivated to combine these teachings because Kunihiro teaches the desirability to stabilize a thrombomodulin-containing solution for lyophilization (abstract) and JP 11-171790 teaches that the addition of the claimed components help to prevent denaturation of the thrombomodulin in a method for preparing the dried composition. One of ordinary skill in the art would have had a reasonable expectation of success in combining these teachings because both references disclose that the claimed agents are compatible with methods for preparing dried thrombomodulin-containing compositions. It would therefore have been obvious to one of ordinary skill in the art to combine the teachings discussed above to arrive at the claimed invention.

25. Claims 1-4, 7-9, 11-15 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kunihiro et al. (US 5,834,028) in view of Zushi (US 5,574,4007). Claims 1 and 2 recite a method of inhibiting foaming of a high-concentrated soluble thrombomodulin-containing solution, which is used in preparing a high-concentrated soluble thrombomodulin-containing solution having a concentration of 10 mg/mL or more by dissolving a soluble thrombomodulin-containing freeze-dried preparation that contains soluble thrombomodulin as an active ingredient, the method being characterized by comprising at least one of: (a) allowing the presence of at least one compound selected from the group consisting of a nonionic surfactant, benzyl alcohol, and chlorobutanol. Claims 3 and 4 recite the method of claim 1, characterized by allowing the presence of a nonionic surfactant in the soluble thrombomodulin-containing freeze-dried preparation or in a dissolving aqueous solution for dissolving the soluble thrombomodulin-containing freeze-dried preparation. Claims 7 and 8 recite the method of claim 1, characterized in that the high-concentrated soluble thrombomodulin-containing solution has a soluble thrombomodulin concentration of 17 mg/mL or more, specifically 25 mg/mL or more. Claim 9 recites the method of claim 1, characterized in that a fluid volume of the high-concentrated soluble thrombomodulin-containing solution prepared by dissolution is in a range of 0.1 mL to 2 mL and an osmotic pressure ratio upon dissolution thereof is in a range of 0.5 to 2.0. Claim 11 recites the method of inhibiting foaming of a high-concentrated soluble thrombomodulin-containing solution according to claim 1, characterized in that: the soluble thrombomodulin-containing freeze-dried preparation is allowed to contain any one of (1) urea or (2) urea and an

amino acid; and a nonionic surfactant is allowed to be present in the soluble thrombomodulin-containing freeze-dried preparation and/or in the dissolving aqueous solution for dissolving the soluble thrombomodulin-containing freeze-dried preparation. Claim 12 recites a method according to claim 1, characterized in that: the soluble thrombomodulin-containing freeze-dried preparation is allowed to contain one or two compounds selected from the group consisting of arginine, glutamic acid, proline, serine, glycine, histidine, asparagine, lysine, phenylalanine, and valine, or salts thereof, trehalose, lactose, and sucrose; further, a nonionic surfactant is allowed to be present in the soluble thrombomodulin-containing freeze-dried preparation and/or in the dissolving aqueous solution for dissolving the soluble thrombomodulin-containing freeze-dried preparation. Claim 13 recites the method of claim 1, characterized in that the nonionic surfactant comprises at least one compound selected from the group consisting of polyoxyethylene sorbitan fatty acid ester, polyoxyethylene/ polyoxypropylene copolymer, polyoxyethylene alkylether, polyoxyethylene fatty acid ester, and polyoxyethylene hydrogenated castor oil. Claim 14 recites the method of inhibiting foaming of a high-concentrated soluble thrombomodulin-containing solution according to claim 1, characterized in that the nonionic surfactant has an existential amount of 0.01 mg or more per 10 mg of the soluble thrombomodulin. Claim 15 recites the method of claim 1, characterized in that the soluble thrombomodulin comprises a peptide that can be dissolved in water in a concentration of 30 mg/mL or more. Claim 18 recites the method of claim 1, characterized in that the soluble thrombomodulin comprises a peptide containing the following sequence, has an action of promoting

activation of protein C with thrombin, and can be dissolved in the absence of a surfactant: an amino acid sequence at positions 19 to 516 of SEQ ID NO. 1 in a sequence listing.

26. Kunihiro teaches a method for preparing a lyophilized (i.e. freeze-dried) composition comprising soluble thrombomodulin and a nonionic surfactant (i.e. a surface-active agent), such as a polyoxyethylene sorbitan fatty acid ester (abstract, col. 9, lines 29-52). Kunihiro teaches that the surfactant may be present in the lyophilized preparation or in the solution that the preparation is dissolved in (col. 11, lines 15-36). In the absence of evidence to the contrary, the composition of Kunihiro may be used to prepare thrombomodulin-containing solutions of the concentrations recited in the claims and with the claimed osmotic pressure upon dissolution. Further, absent evidence to the contrary, the thrombomodulin used in the method of Kunihiro has the claimed solubility in water. Kunihiro teaches the preparations of fluids with fluid volumes of 2 milliliters (col. 20, experiment 5). Kunihiro teaches that the lyophilized composition may comprise arginine or lactose and that the composition may be mixed with sufactant (e.g. polysorbate 80) at the claimed concentration (abstract, col. 20, experiment 5). Kunihiro does not specifically teach the use of a thrombomodulin with the claimed sequence in the method or the addition of urea to the composition.

27. Zushi teaches a peptide sequence for thrombomodulin that is identical to the claimed SEQ ID NO:1 (see Alignment 1, attached). Zushi teaches that urea may be added to a peptide solution to in a process for altering intramolecular structure (col. 26, lines 53-67).

28. Note that a recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim.

29. Moreover, the claimed functions, characteristics, and/or traits must be inherent to the reference composition. The discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new. Thus the claiming of a new use, functions or unknown property that is inherently present in the prior art does not necessarily make the claim patentable (MPEP 2112).

30. At the time of the invention, a method for preparing thrombomodulin comprising nearly all of the claimed elements was known, as taught by Kunihiro. A thrombomodulin was further known at the time of the invention which comprised the claimed sequence, as taught by Zushi. One of ordinary skill in the art would have been motivated to use the peptide taught by Zushi in the process of Kunihiro because Kunihiro teaches that the method can be used with any thrombomodulin (col. 8, lines 15-25). One of ordinary skill in the art would thus have recognized that the thrombomodulin of Zushi would have been acceptable for use in the method of Kunihiro. One of ordinary skill in the art could have used the thrombomodulin of Zushi in the method of Kunihiro with a reasonable expectation of success because the method of Kunihiro could be used with any thrombomodulin. Further, one of ordinary skill in the art would have been motivated to add urea to the composition because Zushi teaches that this is desirable in processes

using the claimed thrombomodulin. Since Zushi teaches that urea is compatible for use with the thrombomodulin, one would have recognized that urea could be added to a composition comprising the thrombomodulin with a reasonable expectation of success. It would therefore have been obvious to one of ordinary skill in the art to combine the teachings discussed above to arrive at the claimed invention.

31. Claims 1-9 and 12-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kunihiro et al. (US 5,834,028) in view of Klokkers-Bethke et al. (US 5,335,769). Claims 1 and 2 recite a method of inhibiting foaming of a high-concentrated soluble thrombomodulin-containing solution, which is used in preparing a high-concentrated soluble thrombomodulin-containing solution having a concentration of 10 mg/mL or more by dissolving a soluble thrombomodulin-containing freeze-dried preparation that contains soluble thrombomodulin as an active ingredient, the method being characterized by comprising at least one of: (a) allowing the presence of at least one compound selected from the group consisting of a nonionic surfactant, benzyl alcohol, and chlorobutanol. Claims 3 and 4 recite the method of claim 1, characterized by allowing the presence of a nonionic surfactant in the soluble thrombomodulin-containing freeze-dried preparation or in a dissolving aqueous solution for dissolving the soluble thrombomodulin-containing freeze-dried preparation. Claim 5 recites the method of claim 1, characterized in that the inner wall of the container to be used in dissolving the soluble thrombomodulin-containing freeze-dried preparation is coated with silicone. Claim 6 recites the method of claim 1, characterized in that the pressure in the container

to be used in dissolving the soluble thrombomodulin-containing freeze-dried preparation is kept at a reduced pressure. Claims 7 and 8 recite the method of claim 1, characterized in that the high-concentrated soluble thrombomodulin-containing solution has a soluble thrombomodulin concentration of 17 mg/mL or more, specifically 25 mg/mL or more. Claim 9 recites the method of claim 1, characterized in that a fluid volume of the high-concentrated soluble thrombomodulin-containing solution prepared by dissolution is in a range of 0.1 mL to 2 mL and an osmotic pressure ratio upon dissolution thereof is in a range of 0.5 to 2.0. Claim 12 recites a method according to claim 1, characterized in that: the soluble thrombomodulin-containing freeze-dried preparation is allowed to contain one or two compounds selected from the group consisting of arginine, glutamic acid, proline, serine, glycine, histidine, asparagine, lysine, phenylalanine, and valine, or salts thereof, trehalose, lactose, and sucrose; further, a nonionic surfactant is allowed to be present in the soluble thrombomodulin-containing freeze-dried preparation and/or in the dissolving aqueous solution for dissolving the soluble thrombomodulin-containing freeze-dried preparation. Claim 13 recites the method of claim 1, characterized in that the nonionic surfactant comprises at least one compound selected from the group consisting of polyoxyethylene sorbitan fatty acid ester, polyoxyethylene/ polyoxypropylene copolymer, polyoxyethylene alkylether, polyoxyethylene fatty acid ester, and polyoxyethylene hydrogenated castor oil. Claim 14 recites the method of inhibiting foaming of a high-concentrated soluble thrombomodulin-containing solution according to claim 1, characterized in that the nonionic surfactant has an existential amount of 0.01 mg or more per 10 mg of the

soluble thrombomodulin. Claim 15 recites the method of claim 1, characterized in that the soluble thrombomodulin comprises a peptide that can be dissolved in water in a concentration of 30 mg/mL or more.

32. Kunihiro teaches a method for preparing a lyophilized (i.e. freeze-dried) composition comprising soluble thrombomodulin and a nonionic surfactant (i.e. a surface-active agent), such as a polyoxyethylene sorbitan fatty acid ester (abstract, col. 9, lines 29-52). Kunihiro teaches that the surfactant may be present in the lyophilized preparation or in the solution that the preparation is dissolved in (col. 11, lines 15-36). In the absence of evidence to the contrary, the composition of Kunihiro may be used to prepare thrombomodulin-containing solutions of the concentrations recited in the claims and with the claimed osmotic pressure upon dissolution. Further, absent evidence to the contrary, the thrombomodulin used in the method of Kunihiro has the claimed solubility in water. Kunihiro teaches the preparations of fluids with fluid volumes of 2 milliliters (col. 20, experiment 5). Kunihiro teaches that the lyophilized composition may comprise arginine or lactose and that the composition may be mixed with sufactant (e.g. polysorbate 80) at the claimed concentration (abstract, col. 20, experiment 5). Kunihiro does not specifically teach the use of a silicone-coated container for the preparation of a thrombomodulin-containing solution or the maintenance of the container at a reduced pressure.

33. Klokkers-Bethke teaches a glass container that is internally coated with silicone for the preparation of a freeze-dried product (abstract). The reference also teaches the

preparation and maintenance of the freeze-dried product at reduced pressure (a vacuum; col. 4, lines 37-50).

34. Note that a recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim.

35. Moreover, the claimed functions, characteristics, and/or traits must be inherent to the reference composition. The discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new. Thus the claiming of a new use, functions or unknown property that is inherently present in the prior art does not necessarily make the claim patentable (MPEP 2112).

36. At the time of the invention, a method for preparing thrombomodulin comprising nearly all of the claimed elements was known, as taught by Kunihiro. It was further known that freeze-dried preparations, such as the one taught by Kunihiro, could be prepared in silicone-coated containers and maintained under reduced pressure, as taught by Klokkers-Bethke. One of ordinary skill would have been motivated to use the method and product of Klokkers-Bethke with the method of Kunihiro because Kunihiro discusses the desirability for the prevention of adsorption of peptides such as thrombomodulin (col. 4, lines 42-64) and Klokkers Bethke teaches that the method and container are suitable for use with proteins and peptides (col. 2, lines 45-54). One of ordinary skill in the art would have had a reasonable expectation of success in

combining these teachings because the method of Kunihiro could be used with any lyophilization method (col. 11, lines 36-44) and the teachings of Klokkers-Bethke could be used with any medicinal substance (col. 3, lines 23-25). It would therefore have been obvious at the time of the invention to combine the teachings discussed above to arrive at the claimed invention.

37. Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sheridan R. MacAuley whose telephone number is (571)270-3056. The examiner can normally be reached on Mon-Thurs, 7:30AM-5:00PM EST, alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on (571) 272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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SRM

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